calculations with the accurate starting point yields a better understanding of the flow profile in an artery based on the transit time.

IN THE SPECIFICATION:

In accordance with 37 C.F.R. §1.121(b)(1), please amend the specification by substituting the following paragraphs for the corresponding paragraphs originally filed, as indicated below. The changes are shown explicitly in the attached "Version with Markings to Show Changes Made."

Replace the first equation on page 2 with the following:

$$(1)\ Q_{rest} = V / \int_{t_0}^{t_1} (T_{r,m}/T_{r,l})dt \propto V / \int_{t_0}^{t_1} (T_{r,0} - T_{r,m})dt \qquad (3.1)$$

Replace the second equation of page 2 with the following:

$$(2)\ Q_{work} = V / \int_{t_0}^{t_1} (T_{w,m}/T_{w,l})dt \propto V / \int_{t_0}^{t_1} (T_{w,0} - T_{w,m})dt \qquad (3.2)$$

Replace the paragraph on page 3 which begins "These quantities" with the following:

These quantities may than be used directly for assessment of the condition of the coronary vessels and the myocardium of the patient, or they may be ratioed as previously discussed to obtain a CFR, *i.e.*, CFR = Q_{work}/Q_{rest}.

Replace the paragraph on page 3 which begins "E.g. in order" with the following:

To obtain a correct measurement, the time has to be measured with some accuracy. Using a simple stop watch, which is a common means of timing, is far too inaccurate for obtaining reliable transit times.

Replace the paragraph on page 3 which begins "Suppose that the" with the following:

Suppose that the flow through a branching vascular bed is constant and equals F, and that a certain well-known amount M of indicator is injected into this bed at site A (see Fig. 7). After some time, the first particles of indicator will arrive at the measuring site B. The concentration of indicator at B, called c(t), will increase for some time, reach a peak and decrease again. The graphic representation of indicator concentration as a function of time is called the indicator dilution curve.

Replace the paragraph on page 3 which begins "Consider M as a" with the following:

Consider M as a large number of indicator particles (or molecules). The number of particles passing at B during the time interval Δt, between t_i and t_{i+1}, equals the number of particles per unit time multiplied by the length of the time interval, in other words: $c(t_i) \cdot F \cdot \Delta t$ (Fig. 8).

Replace the second equation on page 4 with the following:

$$F = \frac{M}{\int_0^\infty c(t) \cdot dt} \qquad (3.3)$$

Replace the paragraph on page 4 which begins "The calculation of" with the following:

The calculation of volume is more complex. For this purpose, the function h(t) is introduced which is the fraction of indicator, passing per unit of time at a measurement site at time t. In other words, h(t) is the distribution function of transit times of the indicator particles. If it is assumed that the flow of the indicator is representative for flow of the total fluid (complete mixing), h(t) is also the distribution function of transit times of all fluid particles. Suppose the total volume of fluid is made up of a very large number of volume elements dV_i which are defined in such a way that dV_i contains all fluid particles present in the system at t=0, with transit times between t_i and t_{i+1}. The fraction of fluid particles requiring times between t_i and t_{i+1} to pass the measurement site, is $h(t_i) \cdot \Delta t$ by definition. Because the rate at which the fluid

particles pass at the measurement site, equals F, the rate at which the particles making up dV_i pass at the measurement site is $F \cdot h(t_i) \cdot \Delta t$. The total volume of dV_i equals the time t_i required for all particles segments in dV_i to pass at the measurement site multiplied by the rate at which they leave. In other words:

Replace the third equation on page 4 with the following:

$$dV_i = t_i \cdot F \cdot h(t_i) \cdot \Delta t \qquad (3.4)$$

Replace the first equation on page 5 with the following:

$$V = F \int_0^\infty t \cdot h(t)dt \qquad (3.5)$$

Replace the paragraph on page 5 which begins "The integral in" with the following:

The integral in the equation above represents the mean transit time T_{mn}, which is the average time needed by one particle to travel from an injection site to a measurement site. Therefore:

Replace the second equation on page 5 with the following:

$$V = F \cdot T_{mn} \qquad (3.6)$$

Replace the third equation on page 5 with the following:

$$F = V/T_{mn} \ ; \ T_{mn} = V/F \qquad (3.7)$$

Replace the paragraph on page 6 which begins "Equation 3.11 describes" with the following:

Equation 3.11 describes how mean transit time T_{mn} can be calculated from the indicator dilution curve c(t). In the assessment of myocardial in which the contrast agent is used as the indicator, because the amount of injected contrast agent is unknown and changing (because of the necessary leakage of the contrast agent into the aorta and the unknown and changing distribution of contrast agent over the different branches of the coronary arterial tree), use of

T_{mn} is advantageous because no knowledge about the amount of injected indicator is necessary.

Replace the paragraph on page 6 which begins "The prior art pressure" with the following:

The prior art pressure pulse triggering of the time measurements, although improving the method considerably, has some drawbacks. For example, the sensitivity in the pressure measurement may not be adequate due to the magnitude of the pulse being quite low; therefore, the accuracy may be negatively influenced.

Replace the paragraph on page 6 which begins "The inventors have" with the following:

The inventors have realized that a previous problem acknowledged in connection with thermo-dilution can be used to an advantage for triggering purposes. Namely, when a bolus of cold saline is injected into a catheter where a wire carrying the sensor unit and electrical leads for signal transmission is located, the lead resistance will be instantly affected by the cold saline by a change in the resistivity. This is a problem, however, because the change must be compensated for in order to arrive at a correct output signal.

Replace the paragraph on page 7 which begins "However, this" with the following:

This compensation can be done, and is one of the issues discussed in our pending Swedish application 9901962-2, corresponding to US provisional 60/136,401.

Replace the paragraph on page 7 which begins "Thus, in accordance" with the following:

Thus, in accordance with the present invention, the resistivity change is recorded as a resistance variation curve. Various parts of the recorded curve, or the entire curve, can be mathematically processed to yield a starting point for the determination for a transit time of the injected liquid. In this way, the accuracy in the time measurement is significantly improved.

Replace the paragraph on page 7 which beings "The method of flow" with the following:

So long as detectable signals are obtained, the method of flow determination according to the invention is advantageous in that it is independent of: (a) the injected amount of bolus liquid; and (b) the temperature of the injected liquid.

Please delete the following paragraph on page 7:

- of the injected amount of bolus liquid

Please delete the following paragraph on page 7:

- of temperature of the injected liquid, so long as detectable signals are obtained

Replace the paragraph on page 7 which begins "Figs. 2a-c" with the following:

Figs. 2a-d are graphs illustrating the resistivity profiles of the electrical leads during measurement;

Replace the paragraph on page 7 which begins "Fig. 7" with the following:

Fig. 7 illustrates an indicator dilution curve obtained in a vascular network;

Replace the paragraph on page 7 which begins "Fig. 8" with the following:

Fig. 8 illustrates calculation of flow in an indicator solution;

On page 9, before the "Detailed Description of the Invention" please add the following paragraph:

Fig. 9 illustrates a curve used in determining the center of mass.

Replace the paragraph on page 8 which begins "In fig. 1" with the following:

In fig. 1 there is disclosed a system suitable for implementation of the present invention. The system comprises a hollow guide catheter insertable into the body of a patient. The distal end of the catheter functions as an outlet for liquid to be passed therethrough. The catheter is located at a point in the artery system where it is desired to know the flow. Inside the catheter a wire is inserted, the distal end of which carries a sensor unit having a temperature sensor and optionally a pressure sensor. Other additional sensors are also conceivable, e.g. pH sensors, ion selective sensors etc. The wire is extended past the distal end of the catheter such that the sensor unit is located at a relatively small distance, e.g. 10 cm, from the catheter outlet.

Replace the paragraph on page 8 which begins "Alternatively, the wire" with the following:

Alternatively, the wire can be inserted as above and positioned in an appropriate position, and then a second catheter can be passed over the wire, inside the guide catheter; the distal end of this second catheter can be positioned in the artery system where it is desired to know the flow. The first catheter will thereby only be used for guiding. This alternative approach can be used if the vessel tree is fairly complex with many narrow blood vessels, making it difficult to position a catheter without the help of the wire.

Replace the paragraph on page 8 which begins "The guide catheter" with the following:

The guide catheter (or the second catheter in the alternative) is provided at the proximal end with an inlet for saline. Preferably, a Luer® lock is provided so that a syringe can easily be connected to the catheter. The sensor unit is coupled to a control unit for the processing of the signals from the sensor unit, said signals being transferred via electrical leads running along the wire.

Replace the paragraph on pages 8-9 which begins "When the above-mentioned" with the following:

When the above-mentioned catheter has been positioned appropriately, it will become filled with blood because of the prevailing pressure difference between the interior of the body and the ambient atmosphere (*i.e.,* the pressure inside the vessel is slightly higher than the

atmospheric pressure externally of the body, P_{body}-$P_{outside}$ > 0). When the wire carrying the sensor has been inserted and the sensor appropriately located at the point of measurement, the operator fills a syringe with a suitable amount of cold saline, say 20°C. The volume to be expelled by the syringe is preferably equal to the volume inside the catheter from the inlet point up to the outlet plus the bolus-dose to be expelled into the flowing blood. The volume of a catheter is commonly about 3 ml, and a suitable bolus-dose could be, for example, 1-3 ml, although the exact volumes will of course differ from case to case.

Replace the paragraph on page 9 which begins "The operator connects" with the following:

The operator connects the syringe to the inlet port and begins injecting the cold saline at a relatively low rate, such that the time to fill the guide catheter all the way up to the outlet will typically take 1-15, preferably 10-15 seconds, although this can vary substantially from case to case outside this interval. The volume of the catheter is known and thus when the operator has expelled a volume corresponding to the catheter volume during the mentioned time period, he will more rapidly expel the last dose, for example, during 0.5 seconds, although this time is not strictly critical.

Replace the paragraph on page 9 which begins "The detection unit" with the following:

The detection unit operates according to the method disclosed in the previously mentioned U.S. provisional 60/136,401. The compensation disclosed therein is based on a switching between measurements of the sensor signal and of the resistance of the leads so as to enable compensation of changes in lead resistance. Thus, when the operator begins injecting the cold saline, the resistivity of the electrical leads will instantly be changed but this will be compensated for so that the detection unit will always deliver a readout of a constant temperature inside the blood vessel at the location of the sensor.

Replace the paragraph on page 9 which begins "For the purpose" with the following:

For the purpose of the invention, the change in resistance of the leads will not be recorded during the initial phase of filling the catheter with saline. But, immediately prior to or at the same time as the operator injects the last bolus-dose into the catheter, the recording of lead signal will be initiated and monitored and also the sensor signal will be recorded and

monitored simultaneously. Because of the rapid injection of the last volume segment of cold saline (from the point t_{start} in Fig. 2a to the point at which the bolus ends, t_{stop}), the cable resistivity will abruptly change since it will experience more cold liquid during a shorter period of time and this will be reflected in a drop in the readout signal as shown in figure 2a. The sensor being located at a relatively short distance from the catheter outlet, for example approximately 10 cm (although this distance is not strictly critical), will be subjected to the cooler bolus-dose of saline a short period of time (on the order of a fraction of a second up to a few seconds) after it has been expelled from the outlet of the catheter. A sensor signal is schematically shown in Fig. 2b, and this signal is recorded and used as the basis for determining the starting point of time measurement.

Replace the paragraph on page 10 which begins "If it can be" with the following:

If it can be assumed that the actual injection of the bolus-dose into the blood-flow will not affect the measurement of the flow at the measurement point, then a calculation as recited under the background of the invention can be performed on the basis of the sensor signal by numeric integration, or by fitting the entire signal from the sensor element to a mathematical function (*e.g.,* natural log, Gamma) to calculate the center of mass of the curve defined by the sensor signal, shown at C in Fig. 2d. Also, a combination of numeric integration and curve fitting can be used. In the latter case, the curve fitting is performed at the portion of the curve approaching the base line, after the cut off point D (see Fig. 2c).

Before the paragraph on page 10 which begins "However, of course" please add the following:

To calculate the center of mass, we assume that it is located at a position x as shown in Fig. 9. The center of mass is found where the area of A_1 = the area of A_2. Accordingly,

$$A_1 = \int_0^x e^{-t/\tau}\,dt \qquad (3.12) \qquad \text{and} \qquad A_2 = \int_x^\infty e^{-t/\tau}\,dt \qquad (3.13)$$

and , therefore:

$$A_1 = -\tau\, e^{-t/\tau} \Big|_0^x = -\tau\, e^{-x/\tau} + \tau \quad \text{and} \quad A_2 = -\tau\, e^{-t/\tau} \Big|_x^\infty = 0 + \tau\, e^{-x/\tau}$$

(3.14) (3.15)

and, therefore, as $A_1 = A_2$, by substitution of equations 3.6a and 3.6b, it is known that

$$-\tau\, e^{-x/\tau} + \tau = \tau\, e^{-x/\tau}$$

it follows, therefore, that $2\,\tau\, e^{-x/\tau} = \tau$.

Dividing both sides of the equation by τ yields $2\, e^{-x/\tau} = 1$ so that $e^{-x/\tau} = 0.5$.

Taking the natural logarithm of both sides yields: $-x/\tau = \ln(1/2)$. It thus follows that:

$$x = -\tau \ln(1/2) = 0.7\tau \qquad (3.16)$$

Replace the paragraph on page 10 which begins "However, of course" with the following:

However, the starting point for the integration (*i.e.*, t=0) must be determined. This point in time can be determined in different ways, using the recorded resistance variation curve. One way to determine t=0 is to register the onset of resistivity reduction. Here the derivative of the curve may be calculated, and if the derivative exceeds a preset value, time measurement is triggered. Another way to determine t=0 is to use the peak value as a starting point for time measurement. Again the derivative, or preferably the second derivative, is calculated and the change in sign is detected. A further usable point is to take the average of the two values, e.g. $(t_{start} - t_{stop})/2$.

Please delete the following paragraph on page 10:

One way is to register the onset of resistivity reduction. Here the derivative of the curve may be calculated, and if the derivative exceeds a preset value, time measurment is triggered.

Please delete the following paragraph on page 10:

Another way is to use the peak value as a starting point for time measurement. Again the derivative, or preferably the second derivative, is calculated and the change in sign is detected.

Please delete the following paragraph on page 10:

A further usable point is to take the average of the two values, e.g. $(t_{start} - t_{stop})/2$.

Replace the paragraph on page 10 which begins "In an alternative" with the following:

In an alternative embodiment the same "triggering" of the time measurement can be used. For the purposes of this invention, "triggering" is defined as the determination of a starting point for the time measurement (*i.e.*, the determination of t=0 for the purpose of integration).

Replace the paragraph on pages 10-11 which begins "In this alternative" with the following:

In this alternative embodiment only the increasing part of the sensor signal (indicated with B' will be used). For this purpose, the mentioned part B' (shown in Fig. 2b) of the sensor signal curve will entirely or partly be fitted to a mathematical function, e.g. $e^{-t/\tau}$, which is an exponential function. The simplest way of doing this is to take the logarithm of the measurement data along B' and to plot this against time. From the slope of the linear portion of that plot, the time constant, τ, of the exponential function can be determined. The point on curve portion B' corresponding to the point on the time axis at $t_{min, sensor} + \tau$ will be center of mass of the exponential curve, which is the point up to which T_{mn} will be calculated from t=0. As derived above, 0.7τ should be used for the identification of the center of mass, but for the purpose of this invention the approximation to τ is adequate. τ can be calculated by fitting the sensor element signal from the point P_s in Fig. 2c up to a point D, where D is the cut-off point, e.g. 10% of the peak value (at P_s).

Replace the paragraph on page 11 which begins "If we assume" with the following:

If we assume that t=0 is equidistant from the points t_{start} and t_{stop}, *i.e.*, $(t_{stop}-t_{start})/2$, then the total mean transit time T_{mn} will be sum

Replace the first equation on page 11 with the following:

$$T_{mn} = (t_{stop}-t_{start})/2 + t_{min, sensor} - t_{stop} + \tau \qquad (3.17)$$

Replace the second equation on page 11 with the following:

$$T_{mn} = t_1 + t_2 + t_3 \qquad (3.18)$$

Replace the paragraph on page 11 which begins "Of the above possible" with the following:

Of the above possible approaches to the determination of T_{mn}, the method discussed in connection with Fig. 2d is the most mathematically accurate. However, the initial flank will very easily be affected by the injection, and the curve fitting may, therefore, be incorrect.

Replace the paragraph on page 11 which begin "The other method" with the following:

The other method (Fig. 2c), where only the portion after the peak is fitted to a curve is more independent of the injection, because the injection is stopped before any calculations are performed on the curve.

Replace the paragraph on page 11 which begins "In Fig. 3 and 4" with the following:

In Fig. 3 and 4, respectively, measurement data on a patient are shown for a hyperemic condition and a resting condition respectively. As can be clearly seen in these figures there is a difference in the time between the minimum of the cable signal and the minimum of the temperature sensor response signal for the two cases. In the hyperemic state the distance is shorter (*i.e.,* the flow is higher) than in the resting condition. It is also clearly visible that the time constant for the increasing portion is slower for the resting condition than for the hypermia condition.

Replace the equation on page 12 with the following:

The CFR is calculated as $CFR = T_{mn,\,rest}/T_{mn,\,hyper}$ (3.19)

Replace the paragraph on page 12 which begins "Finally in figures 5 and 6" with the following:

Finally in figures 5 and 6, respectively, the method according to the invention has been qualitatively evaluated against a reference method which is a determination of CFR by a doppler-technique. In this case however, it should be noted that the doppler-technique has its limitations and is not entirely accurate.

Please add the following paragraphs to the end of page 11:

As previously disclosed in this application, CFR can be obtained by measuring the mean transit time, T_{mn}, for a bolus dose of cold liquid by employing the response curves from lead resistance measurements and a temperature sensor respectively.

For the calculation of T_{mn}, the time constant, τ, of an exponential function $e^{-t/\tau}$ is calculated. It has also been discovered by the inventors that τ itself is correlated to the flow in a coronary vessel, and, therefore, τ itself can be used to determine a valve of CFR where τ_{rest} is the time constant of the temperature sensor response in a resting condition and τ_{hyper} is the time constant of the temperature sensor in a hyperemic condition. Accordingly, CFR = τ_{rest}/τ_{hyper}.

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